

Application Serial No. 09/403,437
Amendment dated December 4, 2003
Reply to Official Action dated June 4, 2003

Amendment to the Claims:

The following Listing of the Claims replaces all prior versions and listings of the claims in this application.

Listing of the Claims:

(?) Claim 1 (Previously Presented): A controlled release pharmaceutical composition comprising:

(a) at least one pharmaceutically active substance having a water contact angle (θ) such that $\cos \theta$ is between +0.9848 and -0.9848;

(b) a first intelligent polymer component; and

(c) a second intelligent polymer component having opposite wettability

GI characteristics to said first intelligent polymer component, said second intelligent polymer component comprising a mixture of hydroxyethylcellulose and hydroxypropyl methyl cellulose, the first and second polymer components being present in a ratio in the range of about 1:100 to about 100:1 by weight,

wherein said first and second polymer components are effective for providing controlled sustained release of said pharmaceutically active substance from said composition for up to at least 20 hours.

Claim 2 (Original): The composition of claim 1, wherein the first intelligent polymer component is more hydrophobic than the second intelligent polymer component.

Claim 3 (Original): The composition of claim 2, wherein the first intelligent polymer component is present in an amount not less than 5% by weight.

Claim 4 (Cancelled).

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Claim 5 (Previously Presented): The composition of claim 1, further comprising at least one pharmaceutically acceptable excipient.

Claim 6 (Original) The composition of claim 5, wherein the excipient comprises 0.25% to 5% by weight of the composition.

Claim 7 (Currently Amended): The composition of claim 1, wherein the at least one excipient is silicon dioxide.

61 Claim 8 (Previously Presented): The composition of claim 1 ~~any one of claims 1 to 7~~, wherein said composition further comprises 0.5% to 15% by weight of at least one surface active agent.

Claim 9 (Original): The composition of claim 8, wherein said surface active agent is sodium lauryl sulfate.

Claim 10 (Original): The composition of claim 1, wherein said composition further comprises 10% to 70% by weight channeling agents.

Claim 11 (Original): The composition of claim 10, wherein said channeling agent is anhydrous lactose.

Claim 12 (Original): The composition of claim 1, wherein said composition further comprises 5% to 30% compression enhancer.

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Claim 13 (Original): The composition of claim 10, wherein said compression enhancer is microcrystalline cellulose.

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Claim 14 (Previously Presented): A controlled release pharmaceutical composition comprising:

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- (a) from about 0.5% to about 70% by weight of a pharmaceutically active substance having a water contact angle (θ) such that $\cos \theta$ is between +0.9848 and -0.9848;
 - (b) not less than about 5% by weight ethylcellulose;
 - (c) about 1:100 to 100:1 hydroxyethylcellulose and hydroxypropyl methyl cellulose by weight;
 - (d) about 0.25% to 5% excipients; and
 - (e) about 0.5% to 15% surface active agents.

Claim 15 (Original): The composition of claim 14, wherein said composition additionally comprises

- about 10% to 70% channeling agents; and
- about 5% to 30% compression enhancers.

Claim 16 (Previously Presented): The composition as claimed in claim 1, made in the form of a compressed tablet.

Claim 17 (Currently Amended): The tableted composition of claim 16, wherein said tableted composition has an an anionic copolymer coating.

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Claim 18 (Original): The tableted composition of claim 17, wherein said copolymer coating comprises methacrylic acid and methyl methacrylate, from about 0% to 25% plasticizer, from about 0% to 25% pigment, from about 0% to 30% glidant and from about 0% to 30% lubricant.

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Claim 19 (Previously Presented): A controlled release composition, the composition comprising a therapeutically effective amount of a pharmaceutically active ingredient having a water contact angle (θ) such that $\cos \theta$ is between +0.9848 and -0.9848; two groups of intelligent polymers having opposing wettability characteristics, one group demonstrating a stronger tendency towards hydrophobicity and present in an amount not less than 5% wt/wt and the other group having a stronger tendency towards hydrophilicity and present in the ratio of about 1:100 and 100:1, the polymers being ethylcellulose (EC) as a more strongly hydrophobic and hydroxyethylcellulose (HEC) and hydroxypropyl methylcellulose (HPMC) as more strongly hydrophilic, about 0.25% to 5% silicon dioxide; and about 0.5% to 15% sodium lauryl sulfate.

Claim 20 (Original): The composition of claim 19, wherein said composition additionally comprises about 10% to 70% anhydrous lactose and about 5% to 30% microcrystalline cellulose.

Claim 21 (Previously Presented): The composition of claim 18, wherein said composition is provided as a tablet and has a coating composition comprising anionic copolymers sufficient to obtain about 0.5 to 15 mg per cm^2 of tablet.

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Claim 22 (Currently Amended): The composition of claim 21, wherein said coating composition additionally comprises from about 0 to 25% plasticizer, about 0 to 25% pigment, about 0 to 30% glidant and about 0 to 30% lubricant.

Claim 23 (Currently Amended): A process for the manufacture of a sustained release composition of pharmaceutically active substance, said process comprising:

(a) admixing a pharmaceutically active substance having a water contact angle (θ) such that $\cos \theta$ is between +0.9848 and -0.9848;

Gl (b) blending the pharmaceutically active ingredient with about 5 to 25% hydroxypropyl methylcellulose, about 1 to 25% hydroxyethylcellulose, about 0.25% to 5% suitable pharmaceutical excipients, about 0.5% to 15% suitable surface active agents, and about 10% to 70% channelling agents in a high shear mixer until a homogeneous mixture is obtained;

(c) granulating the homogeneous blend with isopropyl alcohol (99%) in a planetary or high shear mixer;

(d) drying the wet granules to a loss on drying of about < 3% and organic volatile impurities of isopropyl alcohol about < 15000 ppm;

(e) milling the dry granules to about < 1500 microns;

(f) adding and blending about 5% to 70% of ethylcellulose having 30-60% ethoxyl content and a viscosity of 60- 100 cps to the dry milled granules until a homogeneous blend is obtained;

(g) adding and intimately mixing a lubricant, ~~preferably magnesium stearate~~ and optionally a glidant ~~preferably talc~~ and optionally a compression enhancer;

(h) compressing the lubricated granules into tablets having a hardness of 5-30 Strong Cobb units and a moisture content of about < 5% with a rotary tablet press; and

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(i) optionally encasing the matrix tablet in a GIT "stealth" encasement or a pharmaceutically acceptable film coat.

Claim 24 (Original): The process according to claim 23, wherein said "stealth" encasement comprises anionic copolymer(s) of methacrylic acid and methyl methacrylate and one or more of the following, plasticiser (about 0-25%), titanium dioxide (about 0-25%), pigment (about 0-25%), glidant (about 0-30%), and lubricant (about 0-30%).

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Claim 25 (Previously Presented): The composition of claim 1, encased in a "stealth" encasement formed by a process comprising preparing a first solution of methacrylic acid copolymer type A and/or type B in ethanol, preparing a second solution of PEG 600 in water, adding talc, pigment and titanium dioxide to the first solution and then incorporating the second solution and mixing vigorously under high shear mixing conditions.

Claim 26 (Currently Amended): The composition of claim 1, wherein said pharmaceutically active substance is nifedipine having a specific surface area of $< 0.5 \text{ m}^2/\text{gram}$ or $> 6 \text{ m}^2/\text{gram}$.

Claim 27 (Original): The composition of claim 1, wherein the composition is provided as a tablet which demonstrates the following cumulative percent release dissolution criteria using a pH gradient method of dissolution; 0-40% released in 1 hour in dissolution media of pH 1.50, 0-50% released in 2 hours in dissolution media of pH 4.5, 5-70% released in 2 hours in dissolution media of pH 6.5, 20-100% released in 15 hours in dissolution media of pH 7.5.

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Claim 28 (Previously Presented): The composition of claim 1, wherein the pharmaceutically active substance is selected from the group consisting of nifedipine, glipizide, diltiazem hydrochloride, bupropion, buspirone hydrochloride, tramadol hydrochloride and verapamil HCl.

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Claim 29 (Original): The composition of claim 1, wherein the pharmaceutically active substance is selected from the group consisting of nicardipine, felodipine, captopril, naproxen, diclofenac, terfenadine, pentoxifylline, fenofibrate, glipizide, buspirone, cisapride, verapamil, diltiazem, aciclovir, zidovudine, pilocarpine, moclobemide, lamotrigine, risperidon, clonazepam, nefazodone, lovastatin, simvastatin, pravachol, ketorolac, hydromorphone, morphine, ticlopidine, seligiline, venlafaxine, alprazolam, carbamazepine, divalproex and phenytoin.

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Claim 30 (Previously Presented): A controlled release pharmaceutical composition comprising:

- (a) at least one pharmaceutically active substance having a water contact angle
- (b) such that $\cos \theta$ is between +0.9848 and -0.9848;
- (c) a first intelligent polymer component comprising ethylcellulose
- (d) a second intelligent polymer component having opposite wettability characteristics to said first intelligent polymer component, said second intelligent polymer component comprising a mixture of hydroxyethylcellulose and hydroxypropyl methyl cellulose, the first and second polymer components being present in a ratio in the range of about 1:100 to about 100:1 by weight,

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wherein said first and second polymer components are effective for providing controlled sustained release of said pharmaceutically active substance from said composition for up to at least 20 hours; and

wherein components (a), (b) and (c) are formulated as a homogeneous matrix and said composition has a moisture content of less than 3%.

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Claim 31 (Previously Presented): The composition of claim 1, wherein the first and second polymer components are effective for providing controlled sustained release of such pharmaceutically active substance from said composition for at least 15 hours.

Claim 32 (Previously Presented): The composition of claim 30, wherein the first and second polymer components are effective for providing controlled sustained release of such pharmaceutically active substance from said composition for at least 15 hours.

(?)
Claim 33 (Previously Presented): A controlled release pharmaceutical composition comprising:

(a) at least one pharmaceutically active substance having a water contact angle (θ) such that $\cos \theta$ is between +0.9848 and -0.9848;

(b) a first intelligent polymer component; and

(c) a second intelligent polymer component having opposite wettability characteristics to said first intelligent polymer component, said second intelligent polymer component comprising a mixture of hydroxyethylcellulose and hydroxypropyl methyl cellulose, the first and second polymer components being present in a ratio in the range of about 1:100 to about 100:1 by weight,

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wherein said first and second polymer components are effective for providing controlled sustained release of said pharmaceutically active substance from said composition.

(7)
Claim 34 (Previously Presented): A controlled release pharmaceutical composition comprising:

(a) at least one pharmaceutically active substance having a water contact angle (θ) such that $\cos \theta$ is between +0.9848 and -0.9848;

(b) a first intelligent polymer component comprising ethylcellulose

(c) a second intelligent polymer component having opposite wettability

characteristics to said first intelligent polymer component, said second intelligent polymer component comprising a mixture of hydroxyethylcellulose and hydroxypropyl methyl cellulose, the first and second polymer components being present in a ratio in the range of about 1:100 to about 100:1 by weight,

wherein said first and second polymer components are effective for providing controlled sustained release of said pharmaceutically active substance from said composition; and

wherein components (a), (b) and (c) are formulated as a homogeneous matrix and said composition has a moisture content of less than 3%.

Claim 35 (New): The process according to claim 23, wherein the lubricant comprises magnesium stearate, and/or wherein the glidant comprises talc.